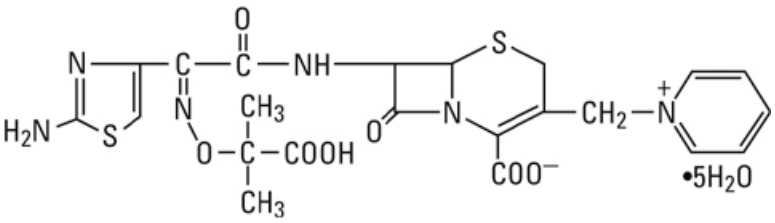
TAZICEF - ceftazidime pentahydrate injection, powder, for solution
Hospira, Inc.

PHARMACY BULK PACKAGE –
NOT FOR DIRECT INFUSION
R_x only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Tazicef (ceftazidime) and other antibacterial drugs, Tazicef (ceftazidime) should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION
Ceftazidime is a semisynthetic, broad-spectrum, beta-lactam antibiotic for parenteral administration. It is the pentahydrate of pyridinium, 1-[[7-[[(2-amino-4-thiazolyl)[(1-carboxy-1-methyl-ethoxy) imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo (4.2.0.)oct-2-en-3-yl] methyl]-,hydroxide, inner salt, [6R-[6α,7β(Z)]]. It has the following structure:



The molecular formula is $C_{22}H_{32}N_6O_{12}S_2$, representing a molecular weight of 636.6.
Tazicef (ceftazidime for injection, USP) is a sterile, dry, powdered mixture of ceftazidime pentahydrate and sodium carbonate. The sodium carbonate at a concentration of 118 mg/gram of ceftazidime activity has been admixed to facilitate dissolution. The total sodium content of the mixture is approximately 54 mg (2.3 mEq)/gram of ceftazidime activity. Solutions of *Tazicef* range in color from light yellow to amber, depending on the diluent and volume used. The pH of freshly reconstituted solutions usually ranges from 5.0 to 7.5.
Tazicef is available in a 6 gram Pharmacy Bulk Package. The contents of this Pharmacy Bulk Package are intended for use by a pharmacy admixture service for addition to suitable parenteral fluids in the preparation of admixtures for intravenous infusion. FURTHER DILUTION IS REQUIRED BEFORE USE.

CLINICAL PHARMACOLOGY
This drug product can be administered intramuscularly, intraperitoneally or by direct intravenous infusion. HOWEVER THE INTENT OF THIS PHARMACY BULK PACKAGE IS FOR THE PREPARATION OF SOLUTIONS FOR INTRAVENOUS INFUSION ONLY.
After IV administration of 500-mg and 1-gram doses of ceftazidime over 5 minutes to normal adult male volunteers, mean peak serum concentrations of 45 mcg/mL and 90 mcg/mL, respectively, were achieved. After IV infusion of 500-mg, 1-gram and 2-gram doses of ceftazidime over 20 to 30 minutes to normal adult male volunteers, mean peak serum concentrations of 42 mcg/mL, 69 mcg/mL and 170 mcg/mL, respectively, were achieved. The average serum concentrations following IV infusion of 500-mg, 1-gram and 2-gram doses to these volunteers over an 8-hour interval are given in Table 1.

Table 1

Ceftazidime	Serum Concentrations (mcg/mL)				
IV Dosage	0.5 hr.	1 hr.	2 hr.	4 hr.	8 hr.
500 mg	42	25	12	6	2
1 gram	60	39	23	11	3
2 grams	129	75	42	13	5

The absorption and elimination of ceftazidime were directly proportional to the size of the dose. The half-life following IV administration was approximately 1.9 hours. Less than 10% of ceftazidime was protein bound. The degree of protein binding was independent of concentration. There was no evidence of accumulation of ceftazidime in the serum in individuals with normal renal function following multiple IV doses of 1 gram and 2 grams every 8 hours for 10 days.

Following IM administration of 500-mg and 1-gram doses of ceftazidime to normal adult volunteers, the mean peak serum concentrations were 17 mcg/mL and 39 mcg/mL, respectively, at approximately 1 hour. Serum concentrations remained above 4 mcg/mL for 6 and 8 hours after the IM administration of 500-mg and 1-gram doses, respectively. The half-life of ceftazidime in these volunteers was approximately 2 hours.

The presence of hepatic dysfunction had no effect on the pharmacokinetics of ceftazidime in individuals administered 2 grams intravenously every 8 hours for 5 days. Therefore, a dosage adjustment from the normal recommended dosage is not required for patients with hepatic dysfunction, provided renal function is not impaired.

Approximately 80% to 90% of an IM or IV dose of ceftazidime is excreted unchanged by the kidneys over a 24-hour period. After the IV administration of single 500-mg or 1-gram doses, approximately 50% of the dose appeared in the urine in the first 2 hours. An additional 20% was excreted between 2 and 4 hours after dosing, and approximately another 12% of the dose appeared in the urine between 4 and 8 hours later. The elimination of ceftazidime by the kidneys resulted in high therapeutic concentrations in the urine. The mean renal clearance of ceftazidime was approximately 100 mL/min. The calculated plasma clearance of approximately 115 mL/min. indicated nearly complete elimination of ceftazidime by the renal route. Administration of probenecid before dosing had no effect on the elimination kinetics of ceftazidime. This suggested that ceftazidime is eliminated by glomerular filtration and is not actively secreted by renal tubular mechanisms.

Since ceftazidime is eliminated almost solely by the kidneys, its serum half-life is significantly prolonged in patients with impaired renal function. Consequently, dosage adjustments in such patients as described in the DOSAGE AND ADMINISTRATION section are suggested.

Therapeutic concentrations of ceftazidime are achieved in the following body tissues and fluids.

Table 2. Ceftazidime Concentrations in Body Tissues and Fluids

Tissue or Fluid	Dose/ Route	No. Patients	Time of Sample Post-Dose	Average Tissue or Fluid Level (mcg/mL or mcg/g)
Urine	500 mg IM	6	0 to 2 hours	2,100.0
	2 grams IV	6	0 to 2 hours	12,000.0
Bile	2 grams IV	3	90 min.	36.4
Synovial fluid	2 grams IV	13	2 hours	25.6
Peritoneal fluid	2 grams IV	8	2 hours	48.6
Sputum	1 gram IV	8	1 hour	9.0
Cerebrospinal				
fluid (inflamed	2 grams q8h IV	5	120 min.	9.8
meninges)	2 grams q8h IV	6	180 min.	9.4
Aqueous humor	2 grams IV	13	1 to 3 hours	11.0
Blister fluid	1 gram IV	7	2 to 3 hours	19.7
Lymphatic fluid	1 gram IV	7	2 to 3 hours	23.4
Bone	2 grams IV	8	0.67 hour	31.1
Heart muscle	2 grams IV	35	30 to 280 min.	12.7
Skin	2 grams IV	22	30 to 180 min.	6.6

Skeletal muscle	2 grams IV	35	30 to 280 min.	9.4
Myometrium	2 grams IV	31	1 to 2 hours	18.7

Microbiology: Ceftazidime is bactericidal in action, exerting its effect by inhibition of enzymes responsible for cell-wall synthesis. A wide range of gram-negative organisms is susceptible to ceftazidime *in vitro* , including strains resistant to gentamicin and other aminoglycosides. In addition, ceftazidime has been shown to be active against gram-positive organisms. It is highly stable to most clinically important beta-lactamases, plasmid or chromosomal, which are produced by both gram-negative and gram-positive organisms and, consequently, is active against many strains resistant to ampicillin and other cephalosporins.
Ceftazidime has been shown to be active against the following organisms both *in vitro* and in clinical infections (see INDICATIONS AND USAGE).
Aerobes, Gram-Negative:*Citrobacter* spp. (including *Citrobacter freundii* and *Citrobacterdiversus*); *Enterobacter* spp. (including *Enterobacter cloacae* and *Enterobacter aerogenes*); *Escherichia coli*; *Haemophilus influenzae*, including ampicillin-resistant strains, *Klebsiella* spp. (including *Klebsiella pneumoniae*); *Neisseria meningitidis*; *Proteus mirabilis*; *Proteus vulgaris*; *Pseudomonas* spp. (including *Pseudomonas aeruginosa*);and *Serratia* spp.
Aerobes, Gram-Positive:*Staphylococcus aureus*, including penicillinase- and non-penicillinase-producing strains; *Streptococcus agalactiae* (group B streptococci); *Streptococcus pneumoniae*, and *Streptococcus pyogenes* (group A beta-hemolytic streptococci).
Anaerobes:*Bacteroides* spp. (NOTE: Many strains of *Bacteroides fragilis* are resistant).
Ceftazidime has been shown to be active *in vitro* against most strains of the following organisms; however, the clinical significance of these data is unknown: *Acinetobacter* spp., *Clostridium* spp. (not including *Clostridium difficile*); *Haemophilus parainfluenzae*; *Morganellamorganii* (formerly *Proteus morganii*); *Neisseria gonorrhoeae*; *Peptococcus* spp.; *Peptostreptococcus* spp.; *Providencia* spp. (including *Providencia rettgeri*, formerly *Proteus rettgeri*); *Salmonella* spp.; *Shigella* spp.; *Staphylococcus epidermidis*; and *Yersinia enterocolitica*.
Ceftazidime and the aminoglycosides have been shown to be synergistic *in vitro* against *Pseudomonas aeruginosa* and the enterobacteriaceae. Ceftazidime and carbenicillin have also been shown to be synergistic *in vitro* against *Pseudomonas aeruginosa*.
Ceftazidime is not active *in vitro* against: methicillin-resistant staphylococci, *Streptococcus faecalis* and many other enterococci, *Listeria monocytogenes*, *Campylobacter* spp., or *Clostridiumdifficile*.
Susceptibility Tests:*Diffusion Techniques:* Quantitative methods that require measurement of zone diameters give an estimate of antibiotic susceptibility. One such procedure[1-3] has been recommended for use with disks to test susceptibility to ceftazidime.
Reports from the laboratory giving results of the standard single-disk susceptibility test with a 30 mcg ceftazidime disk should be interpreted according to the following criteria:
Susceptible organisms produce zones of 18 mm or greater, indicating that the test organism is likely to respond to therapy.
Organisms that produce zones of 15 mm to 17 mm are expected to be susceptible if high dosage is used or if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained.
Resistant organisms produce zones of 14 mm or less, indicating that other therapy should be selected.
Organisms should be tested with the ceftazidime disk, since ceftazidime has been shown by *in vitro* tests to be active against certain strains found resistant when other beta-lactam disks are used.
Standardized procedures require the use of laboratory control organisms. The 30 mcg ceftazidime disk should give zone diameters between 25 mm and 32 mm for *Escherichia coli* ATCC 25922. For *Pseudomonas aeruginosa* ATCC 27853, the zone diameters should be between 22 mm and 29 mm. For *Staphylococcus aureus* ATCC 25923, the zone diameters should be between 16 mm and 20 mm.
Dilution Techniques: In other susceptibility testing procedures, e.g., ICS agar dilution or the equivalent, a bacterial isolate may be considered susceptible if the minimum inhibitory concentration (MIC) value for ceftazidime is not more than 16 mcg/mL. Organisms are considered resistant to ceftazidime if the MIC is ≥64 mcg/mL. Organisms having an MIC value of <64 mcg/mL but >16 mcg/mL are expected to be susceptible if high dosage is used or if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained.
As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard ceftazidime powder should give MIC values in the range of 4 mcg/mL to 16 mcg/mL for *Staphylococcus aureus* ATCC 25923. For *Escherichia coli* ATCC 25922, the MIC range should be between 0.125 mcg/mL and 0.5 mcg/mL. For *Pseudomonas aeruginosa* ATCC 27853, the MIC range should be between 0.5 mcg/mL and 2 mcg/mL.

INDICATIONS AND USAGE

Tazicef (ceftazidime for injection, USP) is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases:

1. **Lower Respiratory Tract Infections,** including pneumonia, caused by *Pseudomonasaeruginosa* and other *Pseudomonas* spp.; *Haemophilus influenzae*, including ampicillin-resistant strains; *Klebsiella* spp.; *Enterobacter* spp.; *Proteus mirabilis*; *Escherichia coli*; *Serratia* spp.; *Citrobacter* spp.; *Streptococcus pneumoniae*; and *Staphylococcusaureus* (methicillin-susceptible strains).

2. **Skin and Skin-Structure Infections**caused by *Pseudomonas aeruginosa*; *Klebsiella* spp.; *Escherichia coli*; *Proteus* spp.; including *Proteus mirabilis* and indole-positive *Proteus* ; *Enterobacter* spp.; *Serratia* spp.; *Staphylococcus aureus* (methicillin-susceptible strains); and *Streptococcus pyogenes* (group A beta-hemolytic streptococci).

3. **Urinary Tract Infections,** both complicated and uncomplicated, caused by *Pseudomonas aeruginosa* ; *Enterobacter* spp.; *Proteus* spp., including *Proteus mirabilis* and indole-positive *Proteus*; *Klebsiella* spp.; and *Escherichia coli*.

4. **Bacterial Septicemia** caused by *Pseudomonas aeruginosa*, *Klebsiella* spp., *Haemophilus influenzae*, *Escherichia coli*, *Serratia* spp., *Streptococcus pneumoniae*, and *Staphylococcus aureus* (methicillin-susceptible strains).

5. **Bone and Joint Infections** caused by *Pseudomonas aeruginosa*; *Klebsiella* spp.; *Enterobacter* spp., and *Staphylococcus aureus* (methicillin-susceptible strains).

6. **Gynecologic Infections,** including endometritis, pelvic cellulitis, and other infections of the female genital tract caused by *Escherichia coli*.

7. **Intra-abdominal Infections,** including peritonitis caused by *Escherichia coli*, *Klebsiella* spp., and *Staphylococcus aureus* (methicillin-susceptible strains) and polymicrobial infections caused by aerobic and anaerobic organisms and *Bacteroides* spp. (many strains of *Bacteroides fragilis* are resistant).

8. **Central Nervous System Infections,** including meningitis, caused by *Haemophilus influenzae* and *Neisseria meningitidis*. Ceftazidime has also been used successfully in a limited number of cases of meningitis due to *Pseudomonas aeruginosa* and *Streptococcus pneumoniae*.

Specimens for bacterial cultures should be obtained before therapy in order to isolate and identify causative organisms and to determine their susceptibility to ceftazidime. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.
Tazicef (ceftazidime for injection, USP) may be used alone in cases of confirmed or suspected sepsis. Ceftazidime has been used successfully in clinical trials as empiric therapy in cases where various concomitant therapies with other antibiotics have been used. *Tazicef* may also be used concomitantly with other antibiotics, such as aminoglycosides, vancomycin and clindamycin, in severe and life-threatening infections and in the immunocompromised patient. When such concomitant treatment is appropriate, prescribing information in the labeling for the other antibiotics should be followed. The dose depends on the severity of the infection and the patient's condition.
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Tazicef (ceftazidime) and other antibacterial drugs, Tazicef (ceftazidime) should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS
Tazicef is contraindicated in patients who have shown hypersensitivity to ceftazidime or the cephalosporin group of antibiotics.

WARNINGS
BEFORE THERAPY WITH *TAZICEF* IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFTAZIDIME, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO *TAZICEF* OCCURS, DISCONTINUE TREATMENT WITH THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, IV FLUIDS, IV ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.
Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ceftazidime, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.
Treatment with antibacterial agents alters the normal flora of the colon and may permit, overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of"antibiotic-associated colitis."
After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an oral antibacterial drug clinically effective against *Clostridium difficile* colitis.

Elevated levels of ceftazidime in patients with renal insufficiency can lead to seizures, encephalopathy, asterixis and neuromuscular excitability (see PRECAUTIONS).

PRECAUTIONS

General:
Ceftazidime has not been shown to be nephrotoxic; however, high and prolonged serum antibiotic concentrations can occur from usual dosages in patients with transient or persistent reduction of urinary output because of renal insufficiency. The total daily dosage should be reduced when ceftazidime is administered to patients with renal insufficiency (see DOSAGE AND ADMINISTRATION). Elevated levels of ceftazidime in these patients can lead to seizures, encephalopathy, asterixis and neuromuscular excitability. Continued dosage should be determined by degree of renal impairment, severity of infection and susceptibility of the causative organisms.
As with other antibiotics, prolonged use of Tazicef (ceftazidime for injection, USP) may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.
Inducible type-1 beta-lactamase resistance has been noted with some organisms (e.g., *Enterobacter* spp., *Pseudomonas* spp., and *Serratia* spp.). As with other extended-spectrum beta-lactam antibiotics, resistance can develop during therapy, leading to clinical failure in some cases. When treating infections caused by these organisms, periodic susceptibility testing should be performed when clinically appropriate. If patients fail to respond to monotherapy, an aminoglycoside or similar agent should be considered.
Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.
Tazicef should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
Distal necrosis can occur after inadvertent intra-arterial administration of ceftazidime.
Prescribing Tazicef (ceftazidime) in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Drug Interactions:
Nephrotoxicity has been reported following concomitant administration of cephalosporins with aminoglycoside antibiotics or potent diuretics, such as furosemide. Renal function should be carefully monitored, especially if higher dosages of the aminoglycosides are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Nephrotoxicity and ototoxicity were not noted when ceftazidime was given alone in clinical trials.
Chloramphenicol has been shown to be antagonistic to beta-lactam antibiotics, including ceftazidime, based on *in vitro* studies and time kill curves with enteric gram-negative bacilli. Due to the possibility of antagonism *in vivo*, particularly when bactericidal activity is desired, this drug combination should be avoided.

Drug/Laboratory Test Interactions:

The administration of ceftazidime may result in a false-positive reaction for glucose in the urine when using Clinitest® tablets, Benedict's solution or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix® or Tes-Tape®) be used.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Long-term studies in animals have not been performed to evaluate carcinogenic potential. However, a mouse micronucleus test and an Ames test were both negative for mutagenic effects.

Pregnancy:
Teratogenic Effects: Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to 40 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Tazicef*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers:
Ceftazidime is excreted in human milk in low concentrations. Caution should be exercised when *Tazicef* is administered to a nursing woman.

Pediatric Use:
(See DOSAGE AND ADMINISTRATION).

Information for Patients:
Patients should be counseled that antibacterial drugs including Tazicef (ceftazidime) should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Tazicef (ceftazidime) is prescribed to treat a bacterial infection,

patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Tazicef (ceftazidime) or other antibacterial drugs in the future.

ADVERSE REACTIONS

Ceftazidime is generally well-tolerated. The incidence of adverse reactions associated with the administration of ceftazidime was low in clinical trials. The most common were local reactions following IV injection and allergic and gastrointestinal reactions. Other adverse reactions were encountered infrequently. No disulfiram-like reactions were reported.

The following adverse effects from clinical trials were considered to be either related to ceftazidime therapy or were of uncertain etiology:

Local Effects, reported in fewer than 2% of patients, were phlebitis and inflammation at the site of injection (1 in 69 patients).

Hypersensitivity Reactions, reported in 2% of patients, were pruritus, rash and fever. Toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have also been reported with cephalosporin antibiotics, including ceftazidime. Immediate reactions, generally manifested by rash and/or pruritus, occurred in 1 in 285 patients. Angioedema and anaphylaxis (bronchospasm and/or hypotension) have been reported very rarely.

Gastrointestinal Symptoms, reported in fewer than 2% of patients, were diarrhea (1 in 78), nausea (1 in 156), vomiting (1 in 500) and abdominal pain (1 in 416). The onset of pseudomembranous colitis symptoms may occur during or after treatment (see WARNINGS).

Central Nervous System Reactions (fewer than 1%) include headache, dizziness and paresthesia. Seizures have been reported with several cephalosporins, including ceftazidime. In addition, encephalopathy, asterixis and neuromuscular excitabiIity have been reported in renally impaired patients treated with unadjusted dosage regimens of ceftazidime (see PRECAUTIONS: General).

Less Frequent Adverse Events (fewer than 1%) were candidiasis (including oral thrush) and vaginitis.

Hematologic: Rare cases of hemolytic anemia have been reported.

Laboratory Test Changes noted during Tazicef (ceftazidime for injection, USP) clinical trials were transient and included: eosinophilia (1 in 13), positive Coombs' test without hemolysis (1 in 23), thrombocytosis (1 in 45), and slight elevations in one or more of the hepatic enzymes, aspartate aminotransferase (AST, SGOT) (1 in 16), alanine aminotransferase (ALT, SGPT) (1 in 15), LDH (1 in 18), GGT (1 in 19) and alkaline phosphatase (1 in 23). As with some other cephalosporins, transient elevations of blood urea, blood urea nitrogen and/or serum creatinine were observed occasionally. Transient leukopenia, neutropenia, agranulocytosis, thrombocytopenia and lymphocytosis were seen very rarely.

Observed During Clinical Practice: In addition to the adverse events reported from clinical trials, the following events have been identified during post-approval use of ceftazidime. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to ceftazidime.

General: Anaphylactic or anaphylactoid reactions, which, in rare instances, were severe (e.g., cardiopulmonary arrest), including laryngeal edema, stridor, and urticaria; pain at injection site.

Hepatobiliary Tract and Pancreas: Hyperbilirubinemia.

Renal and Genitourinary: Renal impairment.

Cephalosporin-Class Adverse Reactions: In addition to the adverse reactions listed above that have been observed in patients treated with ceftazidime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions: Urticaria, colitis, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemorrhage.

Altered Laboratory Tests: Prolonged prothrombin time, false-positive test for urinary glucose, elevated bilirubin, pancytopenia.

OVERDOSAGE

Ceftazidime overdosage has occurred in patients with renal failure. Reactions have included seizure activity, encephalopathy, asterixis and neuromuscular excitability. Patients who receive an acute overdosage should be carefully observed and given supportive treatment. In the presence of renal insufficiency, hemodialysis or peritoneal dialysis may aid in the removal of ceftazidime from the body.

DOSAGE AND ADMINISTRATION

NOTE: This insert is for a Pharmacy Bulk Package and is intended for preparing IV admixtures only. Dosage recommendations for intramuscular or intravenous injection and intraperitoneal use are for informational purposes only.

Dosage: The usual adult dosage is 1 gram administered intravenously every 8 or 12 hours. The dosage and route should be determined by the susceptibility of the causative organisms, the severity of infection and the condition and renal function of the patient.

The guidelines for dosage of Tazicef (ceftazidime for injection, USP) are listed in Table 3. The following dosage schedule is recommended.

Table 3. Recommended Dosage Schedule

	Dose	Frequency

Adults

Usual recommended dose	**1 gram IV**	**q8 or 12h**
Uncomplicated urinary tract infections	250 mg IV	q12h
Bone and joint infections	2 grams IV	q12h
Complicated urinary tract infections	500 mg IV	q8 or 12h
Uncomplicated pneumonia; mild skin and skin structure infections	500 mg to 1 gram IV	q8h
Serious gynecological and intra-abdominal infections	2 grams IV	q8h
Meningitis	2 grams IV	q8h
Very severe life-threatening infections, especially in immunocompromised patients	2 grams IV	q8h
Lung infections caused by *Pseudomonas* spp. in patients with cystic fibrosis with normal renal function*	30 to 50 mg/kg IV to a maximum of 6 grams/day	q8h
Neonates (0– 4 weeks)	30 mg/kg IV	q12h
Infants and children (1 month – 12 years)	30 to 50 mg/kg IV to a maximum of 6 grams/day†	q8h

* Although clinical improvement has been shown, bacteriological cures cannot be expected in patients with chronic respiratory disease and cystic fibrosis.

† The higher dose should be reserved for immunocompromised pediatric patients or pediatric patients with cystic fibrosis or meningitis.

***Impaired Hepatic Function*:** No adjustment in dosage is required for patients with hepatic dysfunction.
Impaired Renal Function: Ceftazidime is excreted by the kidneys, almost exclusively by glomerular filtration. Therefore, in patients with impaired renal function (glomerular filtration rate [GFR]<50 mL/min.), it is recommended that the dosage of ceftazidime be reduced to compensate for its slower excretion. In patients with suspected renal insufficiency, an initial loading dose of 1 gram of ceftazidime may be given. An estimate of GFR should be made to determine the appropriate maintenance dose. The recommended dosage is presented in Table 4.

Table 4. Recommended Maintenance Doses of Tazicef (ceftazidime for injection, USP) in Renal Insufficiency

NOTE: IF THE DOSE RECOMMENDED IN TABLE 3 ABOVE IS LOWER THAN THAT RECOMMENDED FOR PATIENTS WITH RENAL INSUFFICIENCY AS OUTLINED IN TABLE 4, THE LOWER DOSE SHOULD BE USED.

Creatinine Clearance (mL/min.)	Recommended Unit Dose of *Tazicef*	Frequency of Dosing
50 – 31	1 gram	q12h
30 – 16	1 gram	q24h
15 – 6	500 mg	q24h
<5	500 mg	q48h

When only serum creatinine is available, the following formula (Cockcroft's equation)[4] may be used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal function:
Males:

Creatinine clearance (mL/min.) = [Weight (kg) x (140 - age)] / [72 x serum creatinine (mg/dL)]

Females:
0.85 x male value

In patients with severe infections who would normally receive 6 grams of *Tazicef* daily were it not for renal insufficiency, the unit dose given in the table above may be increased by 50% or the dosing frequency increased appropriately. Further dosing should be determined by therapeutic monitoring, severity of the infection and susceptibility of the causative organism.
In pediatric patients as for adults, the creatinine clearance should be adjusted for body surface area or lean body mass and the dosing frequency reduced in cases of renal insufficiency.
In patients undergoing hemodialysis, a loading dose of 1 gram is recommended, followed by 1 gram after each hemodialysis period. Tazicef (ceftazidime for injection, USP) can also be used in patients undergoing intra-peritoneal dialysis and continuous ambulatory peritoneal dialysis. In such patients, a loading dose of 1 gram of *Tazicef* may be given, followed by 500 mg every 24 hours. In addition to IV use, *Tazicef* can be incorporated in the dialysis fluid at a concentration of 250 mg for 2 liters of dialysis fluid.
Note: Generally *Tazicef* should be continued for 2 days after the signs and symptoms of infection have disappeared, but in complicated infections longer therapy may be required.
Administration: See above NOTE concerning the proper use of Pharmacy Bulk Packages.
Intravenous Administration: The IV route is preferable for patients with bacterial septicemia, bacterial meningitis, peritonitis, or other severe or life-threatening infections, or for patients who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure or malignancy, particularly if shock is present or pending.
Intermittent intravenous infusion with a Y-type administration set can be accomplished with compatible solutions. However, during infusion of a solution containing ceftazidime it is desirable to discontinue the other solution.
All vials of *Tazicef* as supplied are under reduced pressure. When *Tazicef* is dissolved, carbon dioxide is released and a positive pressure develops. See RECONSTITUTION.
Solutions of *Tazicef*, like those of most beta-lactam antibiotics, should not be added to solutions of aminoglycoside antibiotics because of potential interaction.
However, if concurrent therapy with *Tazicef* and an aminoglycoside is indicated, each of these antibiotics can be administered separately to the same patient.
RECONSTITUTION
Directions for Proper Use of Pharmacy Bulk Packages:
Note: The Pharmacy Bulk Package is for use in a pharmacy admixture service only. Using aseptic technique, the closure should be penetrated only 1 time after reconstitution using a sterile dispensing set which allows measured dispensing of the contents. Use of a syringe and needle is not recommended as it may cause leakage. The withdrawal of container contents should be accomplished without delay. THE ENTIRE CONTENTS OF THE VIAL SHOULD BE DISPENSED WITHIN 4 HOURS OF INITIAL ENTRY.
A plastic bail attached to the Pharmacy Bulk Package provides a suitable hanging device while dispensing in the pharmacy.
Reconstitute with Sterile Water for Injection according to the following table.

Table 5

Diluent to Be Added	Approx. Avail. Volume	Approx. Avg. Concentration
26 mL	30 mL	1 gram/5 mL
56 mL	60 mL	1 gram/10 mL

The vacuum may assist entry of the diluent. SHAKE WELL.
Insert a gas relief needle through the vial closure to relieve the internal pressure. Remove the gas relief needle before extracting any solution.

COMPATIBILITY AND STABILITY

IMPORTANT: The following chemical stability information in no way indicates that it would be acceptable practice to use this product well after the preparation time. Good professional practice suggests that compounded admixtures should be administered as soon after preparation as is feasible.

Intravenous: Tazicef (ceftazidime for injection, USP) when reconstituted as directed with Sterile Water for Injection, maintains satisfactory potency for 24 hours at room temperature or for 7 days under refrigeration (5°C). Solutions in 0.9% Sodium Chloride Injection in Viaflex® small volume containers that are frozen immediately after reconstitution are stable for 3 months when stored at -20°C. Components of the solution may precipitate in the frozen state and will dissolve upon reaching room temperature with little or no agitation. Potency is not affected. Frozen solutions should only be thawed at room temperature. Do not force thaw by immersion in water baths or by microwave irradiation. For larger volumes where it may be necessary to warm the frozen product (to a maximum of 40°C), care should be taken to avoid heating after thawing is complete. Once thawed, solutions should not be refrozen. Thawed solutions may be stored for up to 8 hours at room temperature or for 4 days in a refrigerator (5°C).

Tazicef (ceftazidime for injection, USP) is compatible with the more commonly used IV infusion fluids. Solutions at concentrations between 1 mg/mL and 40 mg/mL in the following infusion fluids may be stored for up to 24 hours at room temperature or 7 days if refrigerated: 0.9% Sodium Chloride Injection; Ringer's Injection USP; Lactated Ringer's Injection USP; 5% Dextrose Injection; 5% Dextrose and 0.225% Sodium Chloride Injection; 5% Dextrose and 0.45% Sodium Chloride Injection; 5% Dextrose and 0.9% Sodium Chloride Injection; 10% Dextrose Injection.

Tazicef is less stable in Sodium Bicarbonate Injection than in other IV fluids. It is not recommended as a diluent. Solutions of *Tazicef* in 5% Dextrose and 0.9% Sodium Chloride Injection are stable for at least 6 hours at room temperature in plastic tubing, drip chambers and volume control devices of common IV infusion sets.

Ceftazidime at a concentration of 20 mg/mL has been found physically compatible for 24 hours at room temperature or 7 days under refrigeration in Sterile Water for Injection when admixed with: cefazolin sodium 330 mg/mL; heparin 1000 units/mL; and cimetidine HCl 150 mg/mL.

Ceftazidime at a concentration of 20 mg/mL has been found physically compatible for 24 hours at room temperature or 7 days under refrigeration in 5% Dextrose Injection when admixed with potassium chloride 40 mEq/L.

Vancomycin solution exhibits a physical incompatibility when mixed with a number of drugs, including ceftazidime. The likelihood of precipitation with ceftazidime is dependent on the concentrations of vancomycin and ceftazidime present. It is therefore recommended, when both drugs are to be administered by intermittent IV infusion, that they be given separately, flushing the IV lines (with one of the compatible IV fluids) between the administration of these two agents.

Note: Parenteral drug products should be inspected visually for particulate matter prior to administration whenever solution and container permit.

As with other cephalosporins, Tazicef (ceftazidime for injection, USP) powder, as well as solutions, tends to darken depending on storage conditions; within the stated recommendations, however, product potency is not adversely affected.

HOW SUPPLIED

Tazicef in the dry state should be stored at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature] and protected from light. Tazicef (ceftazidime for injection, USP) is a dry, white to off-white powder supplied in vials as follows:

Pharmacy Bulk Vials: equivalent to 6 grams of ceftazidime.
6 gram (tray of 10) NDC 0409-5086-11
Also available as:
Vials: equivalent to 1 gram and 2 grams of ceftazidime.
1 gram (tray of 25) NDC 0409-5082-16
2 gram (tray of 10) NDC 0409-5084-11
"**Piggyback" Vials for IV admixture:** equivalent to 1 gram of ceftazidime.
1 gram (tray of 10) NDC 0409-5083-11
ADD-Vantage® Vials: equivalent to 1 gram and 2 grams of ceftazidime.

1 gram: NDC 0409-5092-16
2 gram: NDC 0409-5093-11

REFERENCES

1. Bauer AW, Kirby WMM, Sherris JC, Turck M. Antibiotic susceptibility testing by a standardized single disk method. *Am J Clin Pathol.* 1966;45:493-496.

2. National Committee for Clinical Laboratory Standards. *Approved Standard: PerformanceStandards for Antimicrobial Disc Susceptibility Tests.* (M2-A3). December, 1984.

3. Certification procedure for antibiotic sensitivity discs (21 CFR 460.1). *Federal Register.* May 30, 1974;39:19182-19184.

4. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16;31-41.

Manufactured by Sandoz GmbH for Hospira Worldwide, Inc., Lake Forest, IL 60045, USA
Made in Kundl, Austria.

ADD-Vantage® Vials manufactured by GlaxoSmithKline for Hospira Worldwide, Inc. Lake Forest, IL 60045, USA
Made in United Kingdom.

 EN-0766 Printed in Austria